ORIGINAL ARTICLE

Choroidal neovascularization associated with extensive macular atrophy with pseudodrusen-like appearance

Néovascularisation choroïdienne dans l’atrophie maculaire extensive avec pseudodrusen

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Summary
Purpose. — Extensive macular atrophy with pseudodrusen-like appearance (EMAP) is a recently described entity. We describe the first observations of choroidal neovascularization (CNV) associated with EMAP in 3 patients.

Methods. — Nineteen consecutive patients with EMAP were retrospectively investigated for the presence of CNV and treatment outcomes. Each patient underwent a complete ophthalmologic examination including color fundus photography, fluorescein angiography (FA), indocyanine green angiography (ICG) and spectral-domain optical coherence tomography (SD-OCT).

Results. — Retrospective analysis revealed choroidal neovascularization in 3 patients (4 eyes) out of 19 patients with EMAP. In these patients, laser photocoagulation or intravitreal injections of ranibizumab led to resolution of retinal exudation with limited functional improvement.

Conclusion. — CNV is a possible complication of EMAP, a recently reported form of macular atrophy resembling geographic atrophy. Laser photocoagulation and anti-VEGF treatment appear to be two valuable therapeutic options.

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Introduction

Extensive macular atrophy with pseudodrusen-like appearance (EMAP) is a recently described entity characterized by bilateral polycyclic, well-delineated chorioretinal atrophy extending to the temporal vascular arcades, with a larger vertical axis, with or without sparing of the fovea, associated with pseudodrusen-like lesions in the middle periphery, and often paving stones lesions in the extreme periphery [1,2]. This atrophy is found in younger patients than those typically diagnosed with dry age-related macular degeneration (AMD). First symptoms usually occur before the age of 55 in EMAP patients, complaining with hemeralopia, reading difficulties despite presbyopia correction and/or difficulty with facial recognition. In contrast to geographic atrophy (GA) in AMD, early onset, bilateral rapid progression of atrophy and early involvement of the foveal zone are observed, leading to a severe visual loss [1]. In the original series reported by Hamel et al., none of the patients diagnosed with EMAP had evidence of choroidal neovascularization (CNV) [1].

Here, we present four eyes clinically diagnosed with EMAP, who underwent treatment for CNV.

Methods

We retrospectively reviewed the charts of all patients diagnosed with EMAP that consecutively presented in the department of ophthalmology, centre hospitalier intercommunal de Créteil, university Paris-Est Créteil, between January 2005 and December 2012. The database of the outpatient clinic (all the patients followed in the center for a macular disease are included in this database) was screened for patients affected by macular atrophy, and among them, we looked for EMAP-affected patients. Hamel et al. [1] diagnostic criteria of EMAP were adopted for selection. These include:

- early onset of bilateral, symmetric macular atrophy in patients less than 55 years of age at time of disease onset;
- rapid involvement of the fovea and of the entire posterior pole up to the temporal vascular arcades;
- numerous drusen-like deposits, surrounding the macular atrophy, spread throughout the posterior pole and the midperiphery;
- paving stone degeneration associated in the far periphery.

In most cases, these patients were referred to our clinic with the diagnosis of early dry AMD, central areolar choroidal dystrophy, or retinal dystrophy. Cases with neovascularization complicating EMAP were investigated.

Results

This retrospective analysis comprised 19 consecutive patients that underwent a complete ophthalmic evaluation including best-corrected visual acuity (BCVA) with ETDRS (Early Treatment Diabetic Retinopathy Study) charts [3], full-field electroretinography (ERG) (according to the guidelines of the International Society for Clinical Electrophysiology of Vision) [4] Goldmann perimetry, fundus biomicroscopy, and multimodal imaging with color fundus imaging (Topcon Imagenet; Ophthalmic Imaging Systems, Tokyo, Japan), infrared (IR), autofluorescence (FAF), Multicolor® (Spectralis, Heidelberg Engineering, starting from 2012) imaging, fluorescein angiography (FA), indocyanine green angiography (ICGA) and time-domain and spectral-domain optical coherence tomography (SD-OCT) (Stratus and Cirrus OCT, Carl Zeiss Meditec; Spectralis, Heidelberg Engineering, Heidelberg, Germany).

We recorded color fundus photography, IR, FAF and OCT using the Topcon Imagenet, Spectralis, Stratus and Cirrus OCT softwares, using the personal information of each patient (surname, first name, date of birth).
All patients were questioned about age at symptoms onset and at presentation, decreased central vision, poor night vision, loss of peripheral vision, and glare sensitivity.

The follow-up period ranged from 1 to 6 years. Patients diagnosed with EMAP (without CNV) were systematically followed every 6 months unless they perceived a major change in their visual acuity. Eyes diagnosed with CNV were followed every month until resolution of exudation. Subsequently, the follow-up was extended to a 3–6 month interval.

Overall, 3 out of 19 patients (4 eyes) presented with CNV complicating EMAP. The CNV type [5], its localization and treatment were documented. The treatments used were laser and anti-VEGF intravitreal injection. When anti-VEGF intravitreal injection was performed, the number of injections necessary to resolve the exudative signs and the follow-up intervals were determined using the same criteria as those used for AMD [5,6].

**Report of cases**

**Case 1**

A woman previously diagnosed with EMAP presented in July 2011, at age 63, with sudden decrease of vision in her right eye (RE); her BCVA was 20/250 in the RE and 20/25 in the LE (Figs. 1 and 2). Her initial symptoms appeared at age 55: these included decreased central vision in both eyes (more pronounced in the RE) and glare sensitivity. ERG revealed decreased photopic and scotopic amplitudes, and Goldmann perimetry showed an absolute central scotoma in both eyes. Fundus biomicroscopy revealed a macular atrophy with a larger vertical axis associated with pseudodrusen-like lesions in the macula and paving stone degeneration on the inferior far periphery of both eyes. FA and OCT showed cystoid macular edema (CME), subretinal fluid and fibrovascular lesion due to an actively leaking supero-macular type 2 CNV associated with hemorrhage. The patient received three intravitreal injections of ranibizumab (0.05 ml/0.5 μg, 1 per month) in her RE, which led to resolution of retinal exudation, without improvement in BCVA.

In August 2012, she presented with sudden vision loss in her LE. BCVA was 20/400 in the RE and 20/250 in the LE. FA and OCT showed subretinal fluid and fibrovascular lesion due to an actively leaking infero-macular type 2 CNV. The patient received three intravitreal injections of ranibizumab (0.05 ml/0.5 μg, 1 per month) in her LE, which led to resolution of retinal exudation, without improvement in BCVA.

In December 2012, after 6 intravitreal injections of ranibizumab in the right eye and 4 in the left eye, her BCVA was 20/400 in the RE, and 20/160 in the LE.

![Figure 1. Case # 1 before treatment—right eye (RE). Color fundus picture of right eye (RE) (A) and left eye (B) showing macular atrophy. Note the hemorrhage on the RE (arrow). Fluorescein Angiograph early (C) and late phase (D) of the RE (July 2011) demonstrating a cystoid macular edema (CME) (arrowhead) due to an actively leaking supero-macular type 2 choroidal neovascularization (arrow). Indocyanine green angiograph early (E) and late phase (F) of the RE. Horizontal (G) optical coherence tomography scan through the macula of the RE showing CME (small arrow), subretinal fluid (asterisks) and the fibrovascular lesion (arrowheads).](image1)

![Figure 2. Case # 1 after treatment—Right eye (RE). Fluorescein Angiograph early (A) and late phase (B) of the right eye (RE) (October 2011) showing resolution of cystoid macular edema (CME) after three intravitreal injections of ranibizumab. Horizontal (C) optical coherence tomography scan through the macula of the RE showing disappearance of CME and subretinal fluid.](image2)
Case 2

A woman presented in June 2007, at age 59, with decrease of vision in her left eye (LE). BCVA was 20/25 in the RE and 20/125 in the left eye (LE) (Figs. 3 and 4). She reported deterioration in her night vision and decreased central vision over the preceding five years. ERG revealed decreased photopic and scotopic amplitudes, and Goldmann perimetry showed an absolute central scotoma in both eyes. Fundus biomicroscopy revealed a macular atrophy with a larger vertical axis associated with pseudodrusen-like lesions in the macula and paving stone degeneration on the far periphery of all four quadrants in both eyes. FA and OCT showed CME and fibrovascular lesion due to an actively leaking temporal-macular type 2 CNV. The patient received three intravitreal injections of ranibizumab (0.05 ml/0.5 μg, 1 per month) in her LE, which led to resolution of retinal exudation, without improvement in BCVA.

In December 2012, after 8 intravitreal injections of ranibizumab in the left eye, her BCVA was 20/40 in the RE, and 20/200 in the LE.

Case 3

A man presented in March 2005, at age 56, with decreased vision in his right eye (RE). BCVA was 20/32 in his RE and 20/25 in his LE (Figs. 5 and 6). The patient complained of poor night and peripheral vision in both eyes since 2000. In 2005, ERG revealed decreased photopic and scotopic amplitudes but no diagnosis was made at this time. Examination with fundus biomicroscopy revealed a macular atrophy with a larger vertical axis associated with pseudodrusen-like lesions in the macula and paving stone degeneration on the inferior far periphery of both eyes. Goldmann perimetry showed an absolute central scotoma in both eyes. FA and OCT showed an actively leaking type 2 CNV located superiorly to the macula. The lesion was treated by focal laser retinal photoablation, and three months later, FA and OCT showed resolution of retinal exudation, without improvement in BCVA (20/32). In December 2008, BCVA decreased to 20/40 due to a recurrence of the CNV activity, and the patient received 2 intravitreal injections of ranibizumab (0.05 ml/0.5 μg, 1 per month), which led to resolution of retinal exudation, with a mild improvement in BCVA three months later (20/25).

In December 2012, his BCVA was 20/400 in the RE, and 20/50 in the LE, and FA and OCT showed no recurrence of the CNV.

Discussion

Here, we described three patients (four eyes) affected by EMAP who presented with choroidal neovascularization. To our knowledge, this is the first description of these pathological associations. EMAP is a recently described entity that associates macular atrophy, pseudodrusen-like lesions, paving stone degeneration in the far periphery, central scotoma, decreased function of cones and rods, and rapid progression in younger patients than those typically seen presenting with AMD.
CNV complicating macular atrophy have been previously reported in the literature [5,7–9]. Querques et al. [5] described how in AMD patients, intravitreal ranibizumab treatment of GA-associated CNVs (in most cases type 1 CNV) provided no BCVA improvement at 24 months of follow-up despite an anatomic response. In the authors’ opinion, limited effectiveness of ranibizumab in these cases was likely due to GA progression. Similarly, we noticed a good anatomical response to intravitreal ranibizumab in our EMAP cases although the functional response was limited [5]. Similarly to the current series, even though in the setting of AMD, Amaro et al. [7] observed good anatomic response with resolution of exudative features following intravitreal anti-VEGF treatment (ranibizumab or bevacizumab) of CNV in eyes with extensive pre-existing GA of the retinal pigment epithelium.

In the current series, CNV complicating macular atrophy was recorded in ∼10% of EMAP eyes (4 out of 38 eyes). Previous published series on AMD, as the main form of macular atrophy complicated by CNV, reported that ∼20% of cases of geographic atrophy (GA) were associated with CNV [8,9].

CNV complicating other macular dystrophies and other atrophic retinopathies have been extensively described in literature [10–18].

In CNV associated with Best vitelliform macular dystrophy, one ranibizumab injection induced total regression of CNV as soon as 1-month following treatment [10]. A resolution of the exudative retinal changes was observed after ranibizumab injections in one patient diagnosed with type 3 CNV associated with adult onset foveomacular vitelliform dystrophy (AOFVD) [11]. Moreover, Mounou et al. showed that after one year of follow-up, ranibizumab succeeded in stabilizing BCVA in patients with CNV associated with AOFVD [12].

Juxtapfoveal choroidal neovascularization has been described in a case of fundus flavimaculatus (FFM) [13]; a retrofoveal recurrence appeared after laser treatment. Type 3 CNV was also seen in FFM [14]; after 3 monthly injections of ranibizumab, BCVA improved from 20/64 to 20/32 and the retinal imaging showed resolution of serous retinal detachment. Intravitreal ranibizumab has also been studied for CNV associated with Stargardt’s disease [15]; three months after the last intravitreal injection of ranibizumab,
eyes and macular thickness was stabilized or decreased in 18 (51.5%) of 35 eyes.

Ranibizumab has been evaluated for the management of Sorsby fundus dystrophy [18]. A patient affected with this rare autosomal-dominant retinal dystrophy, characterized by central vision loss before the fifth decade of life, secondary to chorioidal neovascularization (CNV) and/or pigment epithelium atrophy, had his visual acuity stabilized with 14 injections of ranibizumab.

CNV has also been described in Myopic Choroidal Neovascularization [19,20]. In a meta-analysis from Wang et al., accumulating evidence confirmed that anti-VEGF injections merit utilization as a first-line therapy for myopic choroidal neovascularization [20] given superiority of anti-VEGF over photodynamic therapy in a 24-month period. These findings were confirmed by 2 randomized controlled trials (RCT) and 6 non-RCT studies. No difference was observed between ranibizumab and bevacizumab in two RCTs and one non-RCT study and the estimated visual improvement was two lines on average.

The presence of reticular pseudodrusen in relation with newly diagnosed CNV has been recently investigated [21,22]. Cohen et al. [20] reported high prevalence of reticular pseudodrusen among AMD patients with newly diagnosed CNV (24% of cases). Zweifel et al. [22] found that both soft drusen and reticular pseudodrusen were significantly associated with late AMD.

Boon et al. [23], recently objected that the diagnostic criteria for EMAP could be seen in a variety of macular diseases, such as atrophic age-related macular degeneration, central areolar choroidal dystrophy (CACD), Stargardt disease, retinal dystrophy associated with maternally inherited diabetes and deafness, cone or cone-rod dystrophy, Sorsby fundus dystrophy, and basal laminar drusen. However, the association of different signs (large atrophy with vertical axis, pseudodrusen, rapid evolution in the fifth decade toward legal blindness, absence of pseudovitelliform detachment) in EMAP patients is unique [23]. In the original description by Hamel et al. [1], no patient with EMAP presented CNV. However, in our series, the presence of CNV does not reject the diagnosis of EMAP, given that all other specific diagnostic criteria were detected.

Our study has several limitations, including its retrospective design, the small number of patients included, and the relatively short duration of follow-up.

In conclusion, CNV is a possible complication of EMAP, a recently reported form of macular atrophy resembling GA. Laser photocoagulation and anti-VEGF treatment appear to be two valuable therapeutic options.

Disclosure of interest

The authors declare that they have no conflict of interest concerning this article.

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